REMARKS

Claims 221-225, 232-239, 241-245, 247-251 are currently pending in the application. Claims 221, 224, 232, 237 and 239 are amended. Claims 252-254 are newly added. The amendments find support in the specification and are discussed in the relevant sections below. No new matter is added.

Applicants thank Examiners Whiteman and Lacourciere very much for their time and suggestions in discussing claim amendments on March 23, 2004, and for the consideration of this supplemental amendment.

Applicants have amended base claims 221 and 232, drawn to a dsRNA comprising separate strands, to recite a self complementary double stranded structure that is complementary to less than the full length of an RNA transcript of a mammalian target gene. Claim 249 which is dependent on Claim 221, and newly added claim 253 which is dependent on claim 232, each recite the additional limitation that said double-stranded-structure is fully complementary to less than the full length of an RNA transcript of a mammalian target gene.

Base Claims 224 and 237, drawn to a dsRNA comprising linked strands, already recite the limitation that the dsRNA structure is complementary to less than the full length of an RNA transcript of a mammalian target gene, and Claim 224 already recites the limitation of a dsRNA with self-complementary strands. Claim 237 has been amended to also recite the limitation of a dsRNA with self-complementary strands. These claim amendments were made in order to more clearly differentiate the claimed invention from an embodiment of an oligonucleotide taught by Kmiec et al. This response also addresses the comments regarding the art rejections which were maintained in the final rejection.

Objection to the Claims

The Office Action states that Claims 241-242, 244 and 247 are free of the prior art, but are objected to as being dependent upon a rejected base claim (claim 221). Applicant has amended the base claim to place it in condition for allowance, as discussed below, thereby obviating this objection.

IDS

The Office Action states that the patent (DE 196 18 797 C2) filed in the Information Disclosure Statement filed October 27, 2003 fails to comply with 37 CFR 1.98(a)(3) because it does not include a concise explanation of its relevance, and has not been considered.

Applicant notes that a copy of this patent, which is not in the English language, and a concise explanation of its relevance, was filed in an IDS filed in the spring of 2002 (Paper No. 19 or 20), and has already been considered by the examiner to the extent of the abstract.

Claim Rejections – 35 U.S.C. § 102

NOVELTY OVER ALFONZO ET AL.

Claims 221, 223-224 and 249 were rejected under 102(b) as being anticipated by Alfonzo et al. (Nucleic Acid Research, Vol. 25, 3751-3759, 1997).

The Final Office Action states that "the term 'comprising' and 'having' means that any dsRNA that comprises a region that is complementary to an RNA transcript of a mammalian gene and the region is not more than 49 nucleotides anticipates the claimed product". Applicants have amended base claims 221 and 224, to recite that the encompassed oligoribonucleotide consists of a dsRNA. Claim 249 has been cancelled.

Applicants submit that by substituting the closed language of "consists of" or "consisting of" in place of the open language of "having" or "comprising" in the recitation of the dsRNA of the oligoribonucleotide of the instant claims, the instant claims are precluded from being anticipated by Alfonzo et al.

Applicants note that the structure of the in vivo duplex taught by Alfonzo et al. is ambiguous as to the overall length of the duplexes. In the referenced Figure 2, entitled "Diagram of Models for U insertion/deletion RNA editing", the overall length of the duplex structure is not taught. Specifically, an oligoribonucleotide consisting of a double stranded structure, wherein the structure is not more than 49 nucleotides in length, as encompassed by the instant claims, is not taught by Alfonzo et al.

In view of these amendments and remarks, Applicants respectfully request reconsideration and withdrawal of the rejection.

NOVELTY OVER KMIEC ET AL.

Claims 221, 222, 223, 224, 225, 232, 233, 234, 235, 236, 237, 238, 239, 243, 245 and 248-251 were rejected under 102(e) as being anticipated by Kmiec et al. (U.S. Patent No. 6,537,046).

As in the Alfonzo rejection, the Final Office Action states that "the term 'comprising' and 'having' means that any dsRNA that comprises a region that is complementary to less than the full length of an RNA transcript of a mammalian gene and the region is not more than 49 nucleotides anticipates the claimed product". Accordingly, Applicants have amended base claims 221, 224, 232 and 237 to recite that the encompassed oligoribonucleotide consists of a dsRNA.

Kmiec et al. Does NOT teach and Oligoribonucleotide that Consists of Two Separate Strands .

Kmiec et al. teach a recombinagenic oligonucleobase which is a component of a cell free system for chimeroplasty, (Column 4, lines 39-44). Applicants respectfully submit that the oligonucleobase of Kmiec et al. does not meet the required structural limitations of consisting of two separate strands as required by the oligoribonucleotide recited in base claims 221 and 232. Nowhere in US Patent 6,573,046 does Kmiec et al. teach an oligoribounucleotide that consists of two separate strands that are not linked. In contrast, the oligonucleobase of Kmiec et al. **must** comprise strands that are linked.

In the "Definitions Section", Kmiec et al. defines their disclosed oligonucleobase as follows;

"**An oligonucleobase is a *polymer* of nucleobases, which polymer can hybridize by Watson-Crick base pairing to a DNA having the complementary sequence**", (column 7, lines 18-20, Definitions Section), emphasis added.

"A oligonucleobase compound has a *single* 5' and 3' end nucleobase, which are the ultimate nucleobases of the polymer", (column 7, lines 32-34, Definitions Section), emphasis added.

Furthermore, Kmiec et al. describe a Duplex Mutational Vector (DMV) that comprises their disclosed oligonucleobase as follows:

(i) **"The DMV is a *single oligonucleobase compound* (polymer) of between 24 and 150 nucleobases. Accordingly, the DMV contains a *single* 3' end and a *single* 5' end. The first and second strands can be linked covalently by nucleobases or by non-oligonucleobase linkers.",** (column 9, lines 19-23, emphasis added),

and

(ii) "**Each DMV has a *single* 3' end and a *single* 5' end.**", (column 10, line 40, emphasis added).

In contrast to the single polymer structure of the oligonucleobases taught by Kmiec et al., the oligoribonucleotide recited in instant base claims 221 and 232 consists of two ***separate*** strands. Accordingly, by consisting of ***two*** 5' end nucleobases and ***two*** 3' end nucleobases, the oligoribonucleotide of claims 221 and 232 is thus structurally distinct from the recombinagenic oligonucleobase which "has a ***single*** 5' and 3' end nucleobase", taught by Kmiec et al.

Nowhere in the Kmiec et al. patent is disclosed an oligoribonucleotide consisting of two separate strands. Further, every oligoribonucleobase disclosed by Kmiec et al. throughout the entire specification comprises strands that are linked. By virtue of Kmiec et al.'s complete disclosure, including definitions of an oligonucleobase and a DMV comprising an oligonucleobase, it is clear that Kmiec et al. teach only ***single oligonucleobase polymers*** having ***a single 5' and a single 3' end***, as opposed to the instantly claimed oligoribonucleotide consisting of ***two separate RNA strands*** as recited in base claims 221 and 232. Therefore, Applicants respectively disagree with the conclusion of the final office action that this passage indicates that Kmiec et al. teaches two separate RNA strands.

The following sentence from the final Office action is asserted to indicate that Kmiec et al. teaches two separate strands, **"Furthermore, Kmiec teaches that the first and second strands can be linked covalently (column 9, lines 22-24).".**

Applicant respectfully submits that the quote is taken out of context. Applicants have provided the associated context in underlined italics:

"The DMV is a single oligonucleobase compound (polymer) of between 24-150 nucleobases. Accordingly, the DMV contains a single 3' end and a single 5' end." (Column 9, lines 19-22). **Furthermore, Kmiec teaches that the first and second strands can be linked covalently (column 9, lines 22-24).** ***by nucleobases or by nonoligonucleobase linkers",*** (Column 9, lines 23-24, emphasis added).

In the context of the full quotation, Applicants submit that Kmiec et al. is teaching the ways in which the strands are linked, one way being that the first and second strands can be linked covalently by nucleotide or non-nucleotide linkers. In fact, the linkers connecting the strands were an important component of the invention by Kmiec et al. as evidence by their inclusion in the Abstract. The Abstract testifies that part of the invention taught by Kmiec et al. was their finding that by substituting a nuclease resistant linker such as tetra-2'-O-methyl-uridune, for a nucleotide linker such as tetrathymidine, the activity of the recombinagenic oligonucleobases was increased. In light of the full context of the referenced quote, Applicants disagree with the conclusion in the Office Action that the quote indicates that Kmiec et al teaches separate strands.

The Final Office Action states on page 7: **"Kmiec et al teaches that a strand divided into two chains that are linked covalently through the alternative strand but not directly to each other (column 10, lines 42-67). This indicates that Kmiec teaches two separate RNA strands".**

However, Applicant respectfully disagrees with the Examiner's conclusion on the grounds that the quote is taken out of context. Applicants have provided the entire quote as follows with the added associated context in underlined italics:

"Each DMV has a single 3' end and a single 5' end. In one embodiment the ends are the terminal nucleobases of the strand. In an alternative embodiment, **a strand is divided into two chains that are linked covalently through the alternative strand but not directly to each other"**, (column 10, lines 40-44, emphasis added).

Applicants further note that the two embodiments mentioned above are illustrated by Figures 2 and 1 of the Kmiec et al. patent, respectively. Figure 1 represents a "double hairpin", and Figure 2 represents a "single hairpin" as indicated by the Description of the Figures, (column 3, lines 60-65). According to the Description of the Figures, it appears the examiner is referring to Figure 1, a double hairpin, wherein the strands are linked by a pair of linkers at both ends of the two strands. In a double hairpin, one of the pair of linked strands is divided into two chains. As illustrated by Figure 1, a single strand (strand 'b') is divided into two chains, wherein the two chains are not linked together within the strand. However, one end of each chain of strand 'b' is linked to one end of the alternative strand (i.e. strand 'a'), indicating a structure in which each of the chains of the divided strand is linked to an opposite end of the non-divided strand, but not directly to each other. Therefore, in the above referenced oligonucleobase disclosed by Kmiec et al . column 10, lines 40-44, both strands are linked, and are ***not separate*** as required by instant base claims 221 and 232.

Applicants do not understand how Kmiec's teaching that "one or both strands can contain ribotype nucleobase (column 8, lines 47-48)"as stated on page 7, lines 9-10 of the final Office Action) indicates that Kmiec et al teaches two separate RNA strands. Clarification is respectfully requested.

This hairpin requirement of Kmiec et al. permits Applicants to pursue claims which encompass a double stranded structure consisting of two separate strands. The requirement in claims 221 and 232 of two separate strands (and thus two 5' and 3' ends) is new over Kmiec and thus, for the two stranded structure that Applicants claim, the limitation that the double stranded structure be "fully complementary " to the target gene and/or be self-complementary can also be placed in a dependent claim.

Base Claims 221 and 232 Require an Oligoribonucleotide that Consists of a Self-Complementary Double Stranded Structure that is Fully Complementary to Less than the Full Length of an RNA Transcript and Thus are Strictly Novel over Kmiec et al.

Applicants respectfully submit that the oligonucleobase of Kmiec et al. does not meet the required structural limitations of the instantly recited oligoribonucleotide which consists of a double stranded region that is both ***fully complementary*** to less than the full length of an RNA transcript of a mammalian target gene **AND** that consists of a ***self-complementary*** double stranded structure.

Applicants note that the basis of all the oligonucleobase embodiments taught in Kmiec et al. in their patent entitled "Eukaryotic Use of Improved Chimeric Mutational Vectors" is a recombinagenic oligonucleobase designed to introduce mutations into target DNA, (see lines 1-10 of the Abstract). Kmiec et al. defines a recombinagenic oligonucleobase as:

"**The recombinagenic oligonucleobase is any oligonucleotide or oligonucleotide derivative that can be used to introduce a site specific, predetermined genetic change in a cell**", (column 4, lines 49-52).

The oligonucleobase taught by Kmiec et al. is further characterized in lines 56-60 of column 4, as stated in the first sentence of the instant rejection:

"**Kmiec teaches a recombinagenic oligonucleobase characterized by being a duplex nucleotide, including nucleotide derivatives or non-nucleotide interstrand linkers, and having between 20 and 120 nucleobases or equivalently between 10 and 60 Watson-Crick nucleobase pairs (column 4)**", (page 6 of the final office action).

The structure of the recombinagenic oligonucleobases taught by Kmiec et al. which are designed to introduce mutations into target DNA, is distinct from the structure of the instantly claimed oligoribonucleotides which are designed to specifically inhibit the expression of a mammalian target gene. Specifically, the structural limitations of the claimed oligoribonucleotide include that it ***consist*** of a double stranded region that is both ***fully***

complementary to less than the full length of an RNA transcript of a mammalian target gene **AND** that it ***consist*** of a ***self-complementary double stranded structure***. Further, the oligonucleobase of Kmiec et al. does not meet the required structural limitations of consisting of ***two separate strands*** as required by the oligoribonucleotide recited in base claims 221 and 232, as discussed above.

In order to establish that the referenced Kmiec et al. patent is not prior art, Applicants contrast the structure of the two oligonucleobase embodiments disclosed by Kmiec et al. with the structure of the instantly claimed oligoribonucleotide. In the first Kmiec oligonucleobase embodiment, the two linked strands of the nucleobase are ***not self-complementary***, one strand containing the target sequence and the second strand containing a mismatch—i.e. the desired mutation. In the alternative disclosed oligonucleobase embodiment, the two linked strands are self-complementary, but both strands contain a "mutator region", i.e. a mismatch to introduce a mutation in the target gene, and thus is ***not fully complementary*** to less than the full length of an RNA transcript of a mammalian target gene.

The two disclosed oligonucleobase embodiments as quoted in the Kmiec patent are as follows:

(i) **"In the embodiments wherein the strands are complementary to each other at every nucleobase, the sequence of the first and second strands consists of *at least two regions that are homologous to the target* gene and *one or more regions (the "mutator regions") that differ from the target gene* and introduce the genetic change into the target gene. The mutator region is directly adjacent to homologous regions in both the 3' and 5' directions"**, (column 8, lines 26-34, emphasis added), and

(ii) **"A particularly preferred embodiment of this invention is a DMV *wherein the two strands are not fully-complementary.* Rather the sequence of one strand comprises the sequence of the target DNA to be modified, and the sequence of the alternative strand comprises the different, desired sequence that the user intends to introduce in place of the target sequence"**, (column 11, lines 1-10, emphasis added).

The instant claims require that the recited oligoribonucleotide consist of a self-complementary double stranded structure, wherein said structure is fully complementary to less than the full length of an RNA transcript of a mammalian target gene. In contrast, the linked, self-complementary strands of the first oligonucleobase embodiment taught by Kmiec et al.

contain a mutator region, and thus are ***not*** fully complementary to the target gene as required by the instant claims. Therefore, the first referenced embodiment cannot anticipate the oligoribonucleotide of the instant claims.

Nor can the second oligonucleobase embodiment taught by Kmiec et al anticipate the oligoribonucleotide of the instant claims. The linked strands of the second oligonucleobase embodiment taught by Kmiec et al. are not fully complementary to each other, since the first strand is fully complementary to the target gene and the second strand contains a mismatch relative to the target gene. Because these first and second linked strands are ***not*** self-complementary as required by the oligoribonucleotide recited in instant claims, the second referenced embodiment cannot anticipate the oligoribonucleotide of the instant claims.

Because Kmiec et al. does not teach an oligoribonucleotide that consists of a ***self-complementary*** double stranded structure, wherein said structure is ***fully complementary*** to less than the full length of an RNA transcript of a mammalian target gene, as recited in the instant claims, these claims can not be anticipated by Kmiec et al.

Conclusion

Applicants submit that the dsRNA consisting of two separate RNA strands, encompassed by dependent claims 221 and 232 as amended, are distinct from the single polymer oligonucleotide taught by Kmiec et al. as discussed above.

Further, Applicants submit that by A) amending all the claims to recite closed language such as "consisting of" in the phrase "An oligoribonucleotide consisting of a double stranded structure" in place of the open language of "having" or "comprising", and B) amending base claims 221, 232 and 237 to recite that the two strands of the dsRNA are self-complementary, the instant claims are clearly distinct from the oligonucleobases taught by Kmiec et al. In view of these amendments and remarks, Applicant respectfully requests reconsideration and withdrawal of the rejection.

In view of the foregoing remarks, all issues relevant to patentability raised in the Office Action have been addressed. Applicants respectfully request the withdrawal of rejections over the claims of the present invention.

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